Tetrahydropyridoazepines and Tetrahydropyridoazepinones from the Corresponding Dihydroquinolones

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Received October 7, 1977

The *p*-toluenesulfonate of 7,8-dihydro-5(6*H*)quinolone oxime (**3**) was subjected ot a Beckmann rearrangement. The resulting 2,3,4,5-tetrahydro-1*H*-pyrido[3,2-*b*]azepin-2-one (**4**) was reduced with lithium aluminum hydride affording 2,3,4,5-tetrahydro-1*H*-pyrido[3,2-*b*]azepine (**5**). 5,6-Dihydro-8(7*H*)quinolone (**7**), obtained by oxidation of 5,6,7,8-tetrahydro-8-quinolinol (**6**), was converted into the *p*-toluenesulfonate of 5,6-dihydro-8(7*H*)quinolone oxime (**9**). Similarly the latter compound could be rearranged into 2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*b*]azepin-2-one (**10**) which on reduction produced 2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*b*]azepine (**11**).

J. Heterocyclic Chem., **15**, 249 (1978)

In course of an investigation on the relationship between molecular structure and pharmacological activity of psychotropic compounds, we were led to prepare analogs of tricyclic molecules possessing only one aromatic ring (*cf.* (1)). After some encouraging pharmacological results with the 2,3,4,5-tetrahydro-1*H*-benzazepine and the 2,3,4,5-tetrahydro-1*H*-benzazepin-2-one systems (2), we became interested in the corresponding tetrahydropyridoazepines. To our knowledge the only representatives of this heterocyclic system mentioned in the literature are 1-methyl-2,3,4,5-tetrahydro-6-amino-1*H*-pyrido[4,3-*b*]azepine (3) and 2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*b*]azepine (**11**) (4).

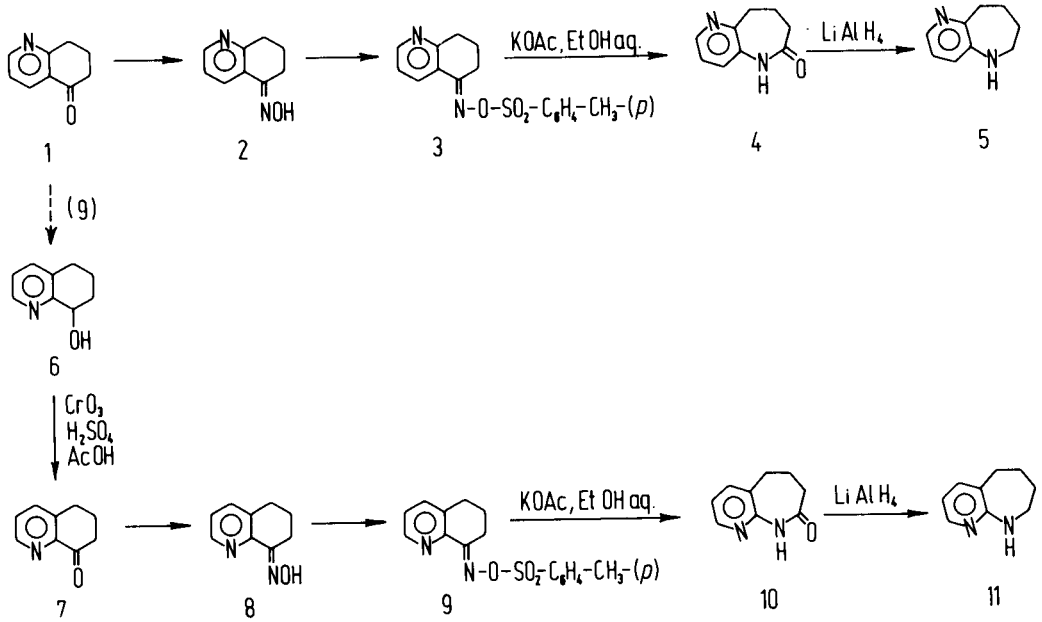
In casting about for a synthesis applicable to the preparation of different isomers of this new ring system, we chose to try the Schmidt degradation (5) and the Beckmann rearrangement (6) on dihydroquinolones because these reactions give good results in the corresponding hydroaromatic series (7-8).

An attempt to rearrange 7,8-dihydro-5(6*H*)quinolone oxime **2** with thionylchloride in dioxane solution (*cf.* (6)) failed. By working in sulfuric acid medium, a small amount of 5-aminoquinoline was obtained in addition to the starting material **2**. Under the conditions of the Schmidt reaction (*cf.* (7)), 7,8-dihydro-5(6*H*)quinolone (**1**) did not react.

Starting from **2** (9) we prepared then the *p*-toluenesulfonate of 7,8-dihydro-5(6*H*)quinolone oxime (**3**), which could be rearranged to 2,3,4,5-tetrahydro-1*H*-pyrido[3,2-*b*]azepin-2-one (**4**). Subsequent reduction of **4** with lithium aluminum hydride furnished 2,3,4,5-tetrahydro-1*H*-pyrido[3,2-*b*]azepine (**5**).

Similarly, 5,6-dihydro-8(7*H*)quinolone (**7**) (obtained by oxidation (*cf.* (10)) of 5,6,7,8-tetrahydro-8-quinolinol (**6**) (9)), after its conversion to 5,6-dihydro-8(7*H*)quinolone oxime (**8**) and the *p*-toluenesulfonate of 5,6-dihydro-8(7*H*)-quinolone oxime (**9**), could be rearranged to 2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*b*]azepin-2-one (**10**). The reduction of this lactam **10** with lithium aluminum hydride yielded 2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*b*]azepine (**11**), which was found to be identical by its physical and particularly

SCHEME



spectral characteristics with the compound prepared by Hawes and Davis (4) *via* intramolecular cyclisation of 4-(3-pyridyl)butylamine.

An attempt to rearrange the oxime **8** with thionyl chloride in chloroform solution (which was successful in the case of 2-benzoylpyridine (11)), failed.

EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 457 spectrometer. Pmr spectra were obtained with a Jeol C-60-H spectrometer using tetramethylsilane as internal reference. Elemental analyses were determined in the section of micro-analysis of the C.N.R.S.

p-Toluenesulfonate of 7,8-Dihydro-5(6*H*)-quinolone Oxime (**3**) (*cf.* (7)).

Compound **2** (1.43 g.), 2.7 g. of *p*-toluenesulfonyl chloride, 20 ml. of acetone and a solution of 0.5 g. of potassium hydroxide in 7 ml. of water were heated under reflux for 30 minutes. The separated crystals were collected, washed with water and recrystallized from ether to yield 85% of **3**, m.p. 110-111°; ir (potassium bromide): 1370, 1195, 1176 cm^{-1} (R-O-SO_2-R); pmr (deuteriochloroform): δ 1.77-2.18 (m, CH_2), 2.44 (s, CH_3), 2.71-3.09 (m, 2 CH_2), 7.13 (d of d, J = 5.0 and 8.0 Hz, pyridine β), 7.33 (d, J = 8.6 Hz, 2H), 7.92 (d, J = 8.6 Hz, 2H), 8.12 (d of d, J = 8.0 and 2.0 Hz, pyridine γ) and 8.52 ppm (d of d, J = 2.0 and 5.0 Hz, pyridine α).

Anal. Calcd. for $C_{16}H_{16}N_2O_3S$: C, 60.80; H, 5.10; N, 8.86. Found: C, 60.91; H, 5.04; N, 8.85.

2,3,4,5-Tetrahydro-1*H*-pyrido[3,2-*b*]azepin-2-one (**4**).

Compound **3** (2.57 g.) and 17 g. of potassium acetate were dissolved in 65 ml. of ethanol and 110 ml. of water. The solution was heated under reflux for 20 hours. The solvent was evaporated at reduced pressure, the solution was rendered alkaline with sodium hydroxide (40%) and the free base extracted into chloroform. The dried extract (dried over sodium sulfate) was evaporated to dryness at reduced pressure to yield 1.10 g. (84%) of **4**, m.p. 163°. After recrystallization from acetone the compound had m.p. 165-165.5°; ir (potassium bromide): 3180 and 3060 (N-H) and 1700 cm^{-1} (C=O); pmr (deuteriochloroform): δ 2.38 (m, 2 CH_2), 3.06 (m, CH_2), 7.15 (d of d, J = 5.0 and 8.0 Hz, pyridine β), 7.35 (d of d, J = 2.0 and 8.0 Hz, pyridine γ), 8.33 (d of d, J = 2.0 and 5.0 Hz, pyridine α) and 9.51 ppm (N-H).

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.63; H, 6.22; N, 17.27. Found: C, 66.64; H, 6.38; N, 17.18.

2,3,4,5-Tetrahydro-1*H*-pyrido[3,2-*b*]azepine (**5**).

A solution of 0.47 g. of **4** in sodium-dried tetrahydrofuran was treated with 1 g. of lithium aluminum hydride and heated under reflux for 4 hours. The excess hydride was decomposed with aqueous methanol and the mixture was extracted with ether. The extract was dried over sodium sulfate, the solvent evaporated, and the residue recrystallized from hexane to yield 70% of **5**, m.p. 80.5-81°, b.p. 158°/14 mm; ir (potassium bromide): 3260 cm^{-1} (N-H); pmr (carbon tetrachloride): δ 1.44-2.00 (m, 2CH_2), 2.80-3.20 (m, 2CH_2), 3.72 (N-H), 6.83 (m, pyridine β), 6.87 (m, pyridine γ) and 7.92 ppm (m, pyridine α).

Anal. Calcd. for $C_9H_{12}N_2$: C, 72.90; H, 8.16; N, 18.91. Found: C, 72.80; H, 8.27; N, 18.81.

5,6,7,8-Tetrahydro-8-quinolinol (**6**) (*cf.* (9)).

A solution of 24 g. of 5,6,7,8-tetrahydroquinoline in 160 ml. of acetic acid was heated with 10 ml. of hydrogen peroxide (30%) at 70-80° for 1 hour. Further 20 ml. of hydrogen peroxide was added and heating continued for 1 hour. After a third addition of the oxidizing agent (30 ml.), the mixture was kept at 70-80° for 15 hours. The acetic acid was removed at reduced pressure. The residue, which was the *N*-oxide of 5,6,7,8-tetrahydroquinoline was heated with 150 ml. of acetic anhydride at 95° for 11 hours. After removal of the acetic anhydride, the residue (8-acetoxy-5,6,7,8-tetrahydroquinoline) was distilled, b.p. 90-127°/1.5-2 mm. This acetate was hydrolyzed with 200 ml. of concentrated hydrochloric acid under reflux for 15 hours. The solution was concentrated, rendered alkaline with sodium hydroxide and the free base extracted into ether. After drying over sodium sulfate, the solvent was evaporated. Recrystallization of the residue (18 g.) from ether afforded 12 g. (44.6%) of **6**, m.p. 64-65°.

5,6-Dihydro-8(7*H*)quinolone (**7**).

A solution of 14.4 g. of **6** in 150 ml. of acetic acid and 16.3 ml. of concentrated sulfuric acid was treated with a solution of 8.6 g. of chromic anhydride in 6 ml. of water and 13 ml. of acetic acid at 20° with stirring. After leaving the reaction mixture at room temperature for several hours, the acetic acid was evaporated under reduced pressure. The residue was dissolved in water, made alkaline with sodium hydroxide, and the free base was extracted with chloroform. The combined extracts were dried over sodium sulfate. After evaporation of the solvent, recrystallization of the residue from a mixture of acetone and ether yielded 7.73 g. (55%) of **7** m.p. 101-102°; ir (potassium bromide): 1695 cm^{-1} (C=O); pmr (deuteriochloroform): δ 2.19 (m, 2H), 2.80 (t, J = 6.0 Hz, 2H), 3.04 (t, J = 6.0 Hz, 2H), 7.36 (d of d, J = 4.4 and 7.9 Hz, pyridine β), 7.68 (d of d, J = 2.0 and 7.9 Hz, pyridine γ) and 8.68 ppm (d of d, J = 2.0 and 4.4 Hz, pyridine α).

Anal. Calcd. for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.29; H, 6.21; N, 9.37.

5,6-Dihydro-8(7*H*)quinolone Oxime (**8**).

This compound was prepared from 7.73 g. of **7** by the method described for **2** (9) (12); the yield was 7.5 g. (84.4%), m.p. 180-182° (recrystallization from methanol); ir (potassium bromide): 3140 (O-H), 1625 (C=N) and 977 cm^{-1} (N-O).

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.70; H, 6.22; N, 17.28. Found: C, 66.58; H, 6.32; N, 17.19.

p-Toluenesulfonate of 5,6-Dihydro-8(7*H*)quinolone Oxime (**9**).

This compound was prepared from 7.5 g. of **8** by the method described for **3**. After completion of the reaction, the acetone was evaporated and the aqueous reaction mixture was neutralized with sodium bicarbonate. The yield of crude product was 15.35 g. A sample was recrystallized from acetone, m.p. 147-148° dec.; ir (potassium bromide): 1370 and 1180 cm^{-1} (-SO_2-O-).

Anal. Calcd. for $C_{16}H_{16}N_2O_3S$: C, 60.80; H, 5.10; N, 8.86. Found: C, 61.20; H, 5.20; N, 8.84.

2,3,4,5-Tetrahydro-1*H*-pyrido[2,3-*b*]azepin-2-one (**10**).

This compound was prepared from 15.35 g. of **9** by the method described for **4**; the heating was continued for 40 hours; the yield (crude product) was 5.68 g. (75.6%), m.p. 144-145° (recrystallization from acetone); ir (potassium bromide): 3200 and 3140 (N-H) and 1680 cm^{-1} (C=O); pmr (deuteriochloroform) δ 2.02-2.70 (m, 4H), 2.81 (t, J = 6.0 Hz, 2H), 7.03 (d of d, J = 5.0 and 7.7 Hz, pyridine β), 7.56 (d of d, J = 7.7 and 2.0 Hz, pyridine γ), 8.40 (d of d, J = 2.0 and 5.0 Hz, pyridine α) and 9.84 ppm (N-H).

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.63; H, 6.22; N, 17.27. Found: C, 67.24; H, 6.47; N, 16.87.

2,3,4,5-Tetrahydro-1*H*-pyrido[2,3-*b*]azepine (**11**).

This compound was prepared from 5.68 g. of **10** by the method described for **5** but in ether solution. The yield was 4.74 g. (91.2%), b.p. 145-151°/14 mm; m.p. 43-44° (recrystallization from ether). The ir and pmr spectra were identical with those described in the literature (4).

Anal. Calcd. for $C_9H_{12}N_2$: C, 72.90; H, 8.16; N, 18.91. Found: C, 72.77; H, 8.13; N, 18.80.

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